Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Best Practice & Research Clinical Endocrinology & Metabolism xxx (xxxx) xxx

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

SARS-CoV-2 infection and female reproductive health: A narrative review

Michelle Maher (Specialist Registrar in Endocrinology)[a,b], Lisa Owens (Consultant Endocrinologist)[a,b,*]

[a] Department of Endocrinology, St James's Hospital, Dublin, Ireland
[b] Department of Medicine, Trinity College Dublin, Ireland

ARTICLE INFO

Article history
Available online xxxx

Keywords:
menstrual cycle
menopause
dysmenorrhoea
infertility
pregnancy
psychological distress

The COVID-19 pandemic has had a profound global impact, affecting people's physical and mental health, and their social and economic circumstances. Mitigation measures have disproportionately affected women. Studies have reported menstrual cycle and psychological disturbance associated with the pandemic. Pregnancy is a risk factor for severe COVID-19 disease. Reports have also demonstrated associations between COVID-19 infection, vaccination and Long COVID syndrome and reproductive health disturbance. However, studies are limited and there may be significant geographical variation. Also there is bias amongst published studies, and menstrual cycle data was not included in COVID-19 and vaccine trials. Longitudinal population based studies are required. In this review we discuss existing data, along with recommendations for further research required in this area. We also discuss a pragmatic approach to women presenting with reproductive health disturbance in the era of the pandemic, encompassing a multi-system assessment of psychological, reproductive health and lifestyle.

Introduction

COVID-19 is a novel, infectious, multi-system disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The COVID-19 pandemic has caused global disruption. It has impacted

* Corresponding author at: Department of Endocrinology, St James's Hospital, Dublin, Ireland.
E-mail address: l.owens15@imperial.ac.uk (L. Owens).

https://doi.org/10.1016/j.beem.2023.101760
1521-690X/

Please cite this article as: M. Maher and L. Owens, SARS-CoV-2 infection and female reproductive health: A narrative review, Best Practice & Research Clinical Endocrinology & Metabolism, https://doi.org/10.1016/j.beem.2023.101760

female reproductive and sexual health and rights in various ways, both at an individual and societal level. The multi-faceted impact of the pandemic on women's health includes menstrual cycle disturbance and psychological disturbance, changes in libido and sexual activity and access to contraception. Studies have also suggested potential reproductive health disturbance from COVID-19 infection, COVID-19 vaccination and Long COVID syndrome. The long term impact of these are unknown.

Men are more likely to die from COVID-19 infection, despite similar numbers of men and women contracting the infection [2]. This has led to speculation that female sex hormones may in some way be protective against severe disease. Sex hormone receptors are ubiquitous, being expressed in nearly all organs and tissues, and play roles far beyond that of reproduction [3]. Many important clinical and immunological differences have been demonstrated between men and women with acute COVID-19 infection; women have lower levels of inflammation, higher lymphocyte counts, and faster antibody responses [4]. Oestradiol is known to have immunomodulatory, antiplatelet and vasodilatory effects [3]. Infection in pregnancy, however, is associated with more severe disease.

Several observational studies have reported menstrual changes related to both COVID-19 infection and COVID-19 vaccination [5,6]. Vaccination against COVID-19 does not impact female fertility [7]. Small-scale studies have found menstrual cycle disturbance in women with Long COVID [8,9]. In fact, Long COVID is more prevalent in women of reproductive age [10]. Female reproductive health disturbance has previously been shown with other viruses, such as HIV and viral hepatitis, which are associated with menstrual cycle alterations, early menopause and miscarriage [11,12]. Direct viral disruption to physiological ovarian steroid hormone production could also theoretically exacerbate symptoms of menopause in women who are already perimenopausal.

There have also been studies reporting reproductive health disturbance relating to the impact of the pandemic and associated mitigation measures and psychological disturbance [13,14]. However it is important to consider that in general menstrual irregularities are common, as is COVID-19 infection and or vaccination [15,16] and that existing observational studies are subject to bias. There are many reasons females may experience menstrual disturbance, such as acute or chronic medical illnesses, mental health conditions, changes in weight, and medications [17–20]. It is not clear how prevalent menstrual cycle changes are, or whether reported menstrual changes reflect normal fluctuations in menstrual symptoms, as opposed to direct effects of COVID-19. Menstrual health in general is a low priority in medical research, and this is no different in relation to COVID-19, as it was not included in trials related to COVID-19 infection, treatment or vaccination.

In this narrative review we present existing data about the impact of COVID-19 infection, the COVID-19 pandemic, COVID-19 vaccination, and Long COVID on female reproductive health. We also review data on the impact of COVID-19 infection in pregnancy, as well as the impact on sexual health and in women undergoing assisted reproductive technology (ART). Given the overall limited amount of published short and long term data in these areas, we recommend important agenda for future research. There is also little in the way of clinical practise guidance, so we will consider a pragmatic clinical approach to menstrual cycle or reproductive health issues arising in this setting.

The impact of SARS-CoV-2 infection on reproductive and sexual health

Emerging evidence suggests that SARS-CoV-2 infection may influence the menstrual cycle. There are a number of plausible means by which SARS-CoV-2 infection may impact the female hypothalamic-pituitary-gonadal (HPG) axis to result in menstrual disturbance [21–25].

SARS-CoV-2 gains cellular access through the angiotensin converting enzyme 2 (ACE2) receptor, which is widely expressed in many tissues including the ovaries and endometrium [26]. As a result, infection with SARS-CoV-2 could theoretically affect ovarian hormone production and endometrial response at menses [22]. In fact, knockdown of ACE2 impairs the endometrial stromal cell decidualisation process through which endometrial cells prepare for embryo implantation [26]. The local presence of the virus in the reproductive tract could also theoretically induce immune disruption. For example, acute infection may alter the phenotype and volume of endometrial leucocytes which could change menstrual blood loss [22,24]. COVID-19 infection may also impact the female reproductive tract through interference with endothelial cell function and systemic haemostasis, resulting in altered menstrual blood loss [21–23,27,28]. Finally, critical illness from COVID-19 may induce hypothalamic amenorrhoea.

However few studies have actually evaluated the impact of acute COVID-19 illness on female reproductive health and those that have are small [29–31]. The Arizona CoVHORT study is a prospective, population-based cohort study which began recruitment in May 2020 [29]. Among 127 women who tested positive for COVID-19, 16% reported a change in their menstrual cycle, the most common of which were irregular menstruation (60%), an increase in premenstrual syndrome symptoms (45%) and infrequent menstruation (35%). The median time interval between a positive SARS-CoV-2 test and the last reported menstrual cycle change was 57.5 days. A cross-sectional Chinese study, conducted in early 2020 observed that 20% of 177 women diagnosed with COVID-19 experienced a significant decrease in menstrual volume, and 19% reported a prolonged menstrual cycle [31]. Furthermore, severally ill patients had longer menstrual cycles than mildly ill patients. However, 84% of participants returned to a normal menstrual volume and 99% returned to their normal menstrual cycle duration with 1–2 months after discharge. In addition, there was no significant difference between sex hormones and anti-Mullerian hormone (AMH) concentrations in the COVID-19 group when compared to age-matched controls. These studies indicated that COVID-related menstrual disturbance may be short-lived and occur as a result of transient sex hormone changes [29,31].

In a further small study, investigating menstrual disturbance in 78 women with COVID-19 infection, there was no difference in menstrual volume, menstrual status, phase of menstrual cycle and dysmenorrhoea between women with non-severe and severe COVID-19 infection [30]. However, women affected by COVID-19 in this study had lower AMH levels and higher serum testosterone and prolactin levels, when compared with healthy controls. This suggests that ovarian injury including a reduction in ovarian reserve could be observed in women with SARS-CoV-2 infection.

In conclusion, the limited available evidence suggests that there may be an association between SARS-CoV-2 infection and transient menstrual changes, along with diminished ovarian reserve. However, data is limited to small cross-sectional studies that were conducted early in the course of the pandemic and show variable results.

Implications to assisted reproductive technologies (ART) in SARS-CoV-2 infection

There is limited clinical data on the ART outcomes following SARS-CoV-2 infection. However, it is plausible that the virus may affect ovarian and endometrial function, as discussed above, along with sperm parameters. There is conflicting evidence as to the presence of SARS-CoV-2 virus in the semen of men with active infection [32,33]. However, men with moderate COVID-19 infection have been shown to have reduced sperm quantity and quality compared to those with mild infection or normal controls [34]. Viral orchitis may cause testicular mesenchymal cell damage, leading to secondary hypogonadism, as has been demonstrated with other viruses [35]. Furthemore, COVID-19 infection is known to activate pro-inflammatory cytokines and provoke and sustain an aberrant systemic inflammatory response [36], which might interfere with folliculogensis and spermatogenesis.

An observational study involving 9 couples undergoing ovarian stimulation for in-vitro fertilisation (IVF) assessed stimulation characteristics and embryological variables before and after recovering from COVID-19 infection [37]. The study did not show any differences between IVF cycles with the exception of a significantly lower proportion of top-quality embryos following COVID-19 infection. This suggests that exposure to SARS-CoV-2 induced systemic inflammation during their development may reduce embryo quality. In this study, couples resumed IVF 8–92 days after recovering from infection therefore the authors of this small study suggest deferral of IVF for 3 months after recovery to reflect the duration of foliculogenesis and spermatogenesis [37].

A further study investigated the impact of asymptomatic or mild, acute SARS-CoV-2 infection on female fertility, embryological outcomes and clinical outcomes in ART treatments [38]. There was a slight decrease in the blastocyst formation rate in the COVID-19 group but there were no differences in the remaining outcomes including ovarian reserve, proportion of mature and fertilised oocytes or high-quality embryos, biochemical and clinical pregnancy rates, early miscarriage rates and implantation rates. The authors postulate that oxidative stress, which has a negative impact on oocyte quality [39], may account for the decrements in blastocyst formation rate but that an additional interaction between the virus and developing embryo is possible.

The negative psychological impact of the suspension of ART treatments during the initial stages of the pandemic should also be considered [40]. Despite data above suggesting that COVID-19 infection itself may influence ART outcomes, there does not appear to be an overall difference in outcomes of ART during the COVID-19 pandemic as compared to the pre-pandemic era [41,42]. Further larger-scale studies are necessary to elucidate fully the direct implications to ART as a result of SARS-CoV-2 infection.

SARS-CoV-2 infection in pregnancy

There does not appear to be an increased rate of SARS-CoV-2 infection in pregnancy relative to the general population [43], and the majority of identified pregnant women are asymptomatic [44]. However, certain comorbidities enhance the risk of infection amongst the pregnant population. The INTER-COVID international study of unvaccinated women showed that obesity, diabetes and insulin-dependent gestational diabetes significantly increase the chance of infection in pregnant women [45]. COVID-19 infection also appears to be more common in later pregnancy. In the UK Obstetric Surveillance System (UKOSS) study, symptomatic infection was primarily diagnosed in the third trimester [46].

Importantly, there is evidence to suggest that pregnant women are at increased risk of severe illness from SARS-CoV-2 infection compared to non-pregnant women particularly in the third trimester. The PregCOVID-19 systematic review consortium demonstrates that pregnant women are more likely to require intensive care admission and mechanical ventilation [44]. However, the overall risk of death remains low and is primarily related to COVID-19 related respiratory or thrombotic disease [47]. The estimated COVID-19 associated maternal mortality rate from the 'Mothers and Babies: Reducing Risk Through Audits and Confidential Enquiries across the UK' (MBRRACE) review was 2.4 per 100,000 [47]. Risk factors associated with more severe infection include being unvaccinated, a body-mass index above 25 kg/m^2, diabetes, hypertension, maternal age of 35 years or above, poor socioeconomic status and being from a minority ethnic background [44,46]. Critically, approximately 98% of pregnant women requiring hospital admission due to severe COVID-19 were unvaccinated [48].

Vertical transmission of the virus is uncommon however [49] and does not appear to be impacted by factors such as mode of delivery, mode of feeding and skin-to-skin contact [50]. There is no apparent association between COVID-19 infection and congenital anomalies [48]. The PregCOVID-19 group however found an approximately doubled risk of stillbirth [44]. This may be explained by widespread placental histological changes as a result of placental infection. A prospective study of 165 unvaccinated women with COVID-19 infection in pregnancy had 6 stillbirths, all of which showed marked histological changes of COVID-19 placentitis, destroying over 75% of the maternal intervillous space [51]. More focal placental changes may be associated with foetal growth restriction [52]. Indeed, there is a near doubling of the risk of low birth weight in the setting of maternal infection [53]. Furthermore, the preterm birth rate in women with symptomatic COVID-19 appears to be 2–3 fold higher than the background rate but the vast majority of these are as a result of obstetric intervention [44,46]. COVID-19 is also associated with increased risk of caesarean section. The UKOSS data shows a 49% caesarean birth rate for women with symptomatic COVID-19 compared to 29% in a representative group from 2018 [46].

In conclusion, SARS-CoV-2 infection in pregnancy is associated with a more severe illness, poorer pregnancy outcomes and carries an associated mortality risk. This data highlights the need to prioritise pregnant women for COVID-19 vaccination on an ongoing basis.

Impact of SARS-CoV-2 vaccination on menstrual cycles

Limited international retrospective and prospective studies have addressed the relationship between COVID-19 vaccination and menstrual cycles [54–61]. Available data suggests that COVID-19 vaccination has a mild transient effect on the menstrual cycle, although the aetiology of this is unclear.

The largest study to-date is an international prospective study that tracked menstrual cycle data from almost 20,000 women using the mobile application 'Natural Cycles' between October 2020 and November 2021 [54]. Compared with unvaccinated individuals, menses length was unaffected but first and second vaccination dose was associated with a mean menstrual cycle increase of 0.71 and 0.56 days respectively. The effect was larger in women who received two doses in the same menstrual cycle, with a mean cycle increase of 3.70 days (2.98–4.42). One cycle after vaccination, the cycle length was similar to

pre-vaccination for individuals who received one dose per cycle, but not yet for women who received two doses per cycle. Two vaccination doses given within the one menstrual cycle suggests that one was given during the follicular phase which was also shown in a further study to be associated with an increased cycle length [61]. It is possible that the HPG axis is affected differently at various stages of the menstrual cycle as a result of the immune response driven by the mRNA vaccine [62,63].

A Norwegian study used online questionnaires to collect retrospective menstrual data on 5688 women of reproductive age before and after vaccination [56]. After both doses of the vaccine women reported heavier bleeding than usual. There was also an increased risk of additional menstrual disturbances including longer duration menses. Another cross-sectional retrospective study of 14,153 women who completed their vaccination course at least three months prior, showed that 78% of women reported menstrual changes post-vaccination, included heavier menstrual bleeding (43%), increased menstrual pain (41%), delayed menstruation (38%), fewer days of menstrual bleeding (34.5%) and shorter cycle length (32%). Each of these studies describe temporary and self-limiting menstrual cycle disturbance, whilst some other studies do not observe a positive association between vaccination and menstrual cycle disturbance at all [57].

Unfortunately, menstrual data was not included in most large-scale COVID-19 studies, including vaccine trials [22], which is even more critical given that these are newly introduced mRNA-based vaccines [57]. Further studies are required to assess immunological influences on menstruation in this setting.

The impact of the COVID-19 pandemic on female reproductive health

Evidence to-date suggests that there is an association between the COVID-19 pandemic and changes in menstrual patterns and sexual behaviours. This is consistent with previous reports which have shown an association between complex social crises (e.g. natural disasters, war) and disturbance of menstrual and sexual function in the setting of psychological distress [64,65].

Numerous studies have reported on menstrual cycle disruption during the pandemic [13,14,57,66–75]. Two recent systematic reviews have utilised data from the highest quality studies to characterise the relationship between the pandemic and menstrual disturbance [76,77]. A systematic review and meta-analysis incorporating data from six studies, found a significant association between lockdown and changes in the menstrual cycle for 21729 women of reproductive age [76]. Similarly, the second systematic review which included data from thirteen studies, found that menstrual disorders were a more common during the pandemic as compared to pre-pandemic, and that women affected by pandemic-related stress were more prone to changes in the duration of their menses, and reported increased rates of dysmenorrhoea and heavier menstrual bleeding [77]. A Hungarian study found no association between vaccination or infection and menstrual cycle changes, but found that menstruation length increased whilst regularity of the menstrual cycle decreased during the peak of the pandemic and this correlated with the severity of depression [57]. The known vulnerability of the female HPG axis to psychosocial stress is a key consideration when assessing the effects of the COVID-19 pandemic on the menstrual cycle [78–80].

In the early stages of the pandemic, Ozimek et al. observed many changes in menstrual cycles, including menstruation duration, cycle length and significant perceived stress [70]. Subsequently, two cross-sectional survey-based studies conducted in Ireland in 2020 and 2021 demonstrated wider variability in minimum and maximum menstrual cycle length, along with increases in self-reported dysmenorrhoea, missed periods, heavy menstrual bleeding and pre-menstrual symptoms (PMS) compared to pre-pandemic [13,14]. The latter study, showed that poor sleep quality was an independent predictor of overall change in menstrual cycle and missed periods during the pandemic, whilst increased anxiety was independently associated with painful periods and worsening of PMS [13]. Similarly, a study conducted of Turkish healthcare workers found that depression, anxiety and stress were positively correlated with irregular menstrual cycles [73]. In contrast, a retrospective cohort study which examined raw data from over 18,000 women using a menstrual tracking smartphone app did not show any evidence of population-level changes to ovulation and menstruation when comparing data between 2019 and 2020 [71]. This study limits recall bias, however it was carried out in the early stages of the pandemic, and there was minimal representation from women of lower educational and socioeconomic

status, with whom irregular menstruation and higher perceived stress have previously been associated [15].

In conclusion, studies suggest that many women have experienced menstrual disturbance during the COVID-19 pandemic, and this is associated with psychological stress. However most of these studies are short-term and rely on self-reported cross-sectional data, which can be subject to reporting bias, and these limitations which must be considered when interpreting the results of existing studies [22].

The COVID-19 pandemic also appears to have had an overall negative impact on female sexual function [13,72,74,81]. 54% of 1335 women surveyed in Ireland in April 2021 reported a reduction in their libido since the onset of the pandemic [13]. A cross-sectional Turkish study reported a decrease in quality of sexual life (as measured by the female sexual function index (FSFI) score, despite increased sexual desire and frequency of sexual intercourse compared to prior to the pandemic [74]. A similar Italian study demonstrated an increase in female sexual distress scale scores, but with decreased frequency of sexual intercourse and FSFI scores, in conjunction with reduced quality of life [81].

Existing research is also suggestive of an overall decline in female contraceptive use during the pandemic, likely attributable to changes in sexual behaviour as a result of social distancing, along with reduced access to healthcare [72,74,82–85]. An Italian-based study showed that 51% of non-cohabiting or single women discontinued short-acting reversible contraception but 47% of them continued their sexual activity resulting in a rise in unplanned pregnancies [82]. Further research is necessary to assess the ongoing impact of the pandemic on sexual behaviour and contraceptive practices as many of the published studies were conducted in the early stages of the pandemic, when restrictions were in place.

Female reproductive health in long COVID

Long COVID is most prevalent amongst premenopausal women, affecting twice as many women as men [10]. In the USA, long COVID also disproportionately impacts transgender people [86]. Reproductive health disturbance is reported, but poorly studied, amongst females with long COVID. In addition, menstruation or the premenstrual period, the time of cyclical nadir of oestrogen, may trigger symptoms of long COVID [8], suggesting that the wider symptoms of long COVID may be partly mediated by ovarian steroid hormone fluctuation.

An international online survey of those with long COVID reported data from 1792 reproductive aged women [8]. 36% reported overall menstrual disturbance- 26% reported irregular menstrual cycles and 20% reported heavy menses. This study also included 1124 women over the age of 49, of whom 5% experienced postmenopausal bleeding, and included 938 women between the ages of 40–49, of whom 3% reported early menopause.

A study of 483 women in Iraq and Jordan who had COVID-19 infection [87] demonstrated a change in menstrual cycle duration and change in blood volume in 47%, and a change in length of menses in 42%. Half of 460 women surveyed in the UK self-reported that their menstrual period had stopped or changed since experiencing COVID-19 infection [9]. It is important to note though that this association between long COVID and reproductive health disturbance demonstrated in observational studies does not prove causation.

Disruption of ovarian steroid hormone production associated with SARS-CoV-2 infection in women around the age of menopause could theoretically exacerbate symptoms of menopause [88]. There is a significant overlap between symptoms of menopause/perimenopause and long COVID (e.g. fatigue, sleep disturbance, brain fog, palpitations). A survey in the UK reported that 70% of women attributed their long COVID symptoms to menopause or their menopausal symptoms to long COVID [9]. Failure to recognise and diagnose perimenopause could lead to a lost opportunity to manage debilitating symptoms with menopausal hormone therapy [88], therefore awareness with regards to the potential overlap of long COVID and menopausal symptoms is important.

In conclusion, observational studies demonstrate an association between long COVID and menstrual cycle disturbance. In addition, it may be difficult to differentiate between the wider symptoms of long COVID and perimenopause, resulting in suboptimal treatment. Further longitudinal research is required to explore the links between long COVID and the female reproductive hormones.

Clinical practice recommendations

Given the broad nature of the potential causes of reproductive health disturbance in the era of the COVID-19 pandemic, as well as likely variation in impact depending on geographic location and socio-economic circumstance, and the lack of clinical practice guidance, or longitudinal studies or studies assessing potential interventions, it is difficult to make for clinicians to make recommendations to women that they review in this context.

Studies show that the COVID-19 vaccine may be associated with mild and transient menstrual cycle change. Healthcare providers should advise women who are concerned that menstrual cycle changes may occur after COVID-19 vaccination; their cycle may be longer and bleeding may be heavier. However they should be reassured that changes are mild and short lived, lasting usually for 1–2 cycles and that temporary disruption to cycles is much less risk to overall health than the potential impact of COVID-19 infection, especially in women of reproductive age, as severe disease can be harmful to pregnant women and their babies. They should also be reassured that there is no evidence that fertility or pregnancy outcomes are negatively impacted by vaccination. It is important that misinformation does not promote vaccine hesitancy. Women who have persistent cycle changes after the vaccination should seek medical advice, as they may incidentally have an underlying reproductive health condition.

In general women may present for the first time with underlying reproductive health conditions which may be coincidental but are erroneously attributed to COVID-19 infection or vaccination or long COVID, due to their high prevalence, e.g. Polycystic Ovary Syndrome (PCOS) or Endometriosis. Additionally, the pandemic may have exacerbated certain conditions. Women with PCOS, for example, may experience worsening symptoms of the condition during the pandemic due to weight gain, psychological distress, and reduced access to medical and cosmetic treatments. Psychological distress resulting from the pandemic may have caused increased prevalence of hypothalamic amenorrhoea, in fact studies did report an increase in the number of missed periods in the early stages of the pandemic. Also the media coverage of the impact of the vaccine and the disinformation around fertility may have shone a spotlight on this, so women may present for the first time with pre-existing reproductive conditions.

We therefore recommend a thorough assessment for signs and symptoms of common endocrine and gynaecological conditions, such as PCOS and endometriosis, as well as perimenopause. Assessment should include assessment of weight and body mass index, change in or discontinuation of hormonal contraception, and further testing will depend on predominant symptoms but may include blood testing e.g. FSH, LH, oestradiol, prolactin, androgens, thyroid function. Women should be counselled appropriately regarding sexual health and contraception.

Women who experience transient menstrual cycle change that has resolved and is attributed to the psychological impact of the pandemic, should be reassured that this is unlikely to impact their long-term reproductive health. Women who report persistent cycle disturbance without features of an obvious underlying biological cause, baseline blood tests as outlined above should be considered, as well as an objective assessment of psychological health. Treatment should depend on predominant symptoms and also be based on local guidance. Lifestyle advice regarding weight, diet, exercise and alcohol intake should be provided.

Summary

Results from observational studies suggest that the COVID-19 pandemic has impacted women's menstrual cycles, resulting in worsening painful and heavy menstrual bleeding, missed periods, changes in cycle duration and worsening pre-menstrual symptoms. Studies show a link between this menstrual disturbance and psychological distress. It is unknown if this menstrual disturbance is transient, as longitudinal data encompassing the duration of the pandemic has not been published. Studies have also shown reduced frequency of sexual activity and libido, but again the permanency of this is unknown. The pandemic, at least in the early stages, has been associated with reduced use of contraceptives. SARS-CoV-2 and Long COVID may be associated with reproductive health disturbance, and studies also show that the COVID-19 vaccine can cause temporary menstrual disruption. The impact of all of above on fecundity are unknown and are likely to vary depending on economic and geographic factors.

Practice points

- Temporary menstrual cycle changes may occur after COVID-19 vaccination, including longer cycle length and heavier bleeding. Women should be reassured that these changes typically last for 1–2 cycles.
- There is no evidence that fertility or pregnancy outcomes are impacted by vaccination against COVID-19. Healthcare professionals and policy makers should inform women of this.
- For women experiencing persistent menstrual cycle disturbance, we recommend a thorough multidisciplinary assessment including assessment for underlying gynaecological/endocrine conditions, psychological assessment, assessment of weight, diet, lifestyle.
- Healthcare providers should be aware that pregnant women who are older, have co-morbidities, are from ethnic minorities, are obese or experience socio-economic deprivation are more likely to experience severe COVID-19 infection. Women planning pregnancy should ensure they are vaccinated against COVID-19 infection.

Research agenda

We recommend that future studies should focus on the following areas, and should incorporate large-scale longitudinal studies in different geographical locations:

- The short and long-term effects of exposure to Sar-CoV-2 and pandemic mitigation measures on reproductive health and fertility.
- Associations between long COVID, menstrual cycle disturbance and co-existing reproductive health conditions.
- Assessment of interventions that could be adopted to recognise, modify and treat/reverse the negative impact on reproductive health. For example in cases associated with psychological disturbance, a trial of digital cognitive behavioural therapy.
- Birth trends, ART and pregnancy outcomes in the years during and following the COVID-pandemic compared with before.
- Research to elucidate the epidemiological basis, as well as the underlying biological mechanisms for sex-differences in Long COVID

Role of the funding source

N/a, no external funding was received.

Conflict of interest statement

The authors do not have any conflicts of interest to declare.

References

[1] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62.
[2] Nguyen NT, Chinn J, De M. Ferrante, et al., *Male gender is a predictor of higher mortality in hospitalized adults with COVID-19.*. PLoS One 2021;16(7):e0254066.
[3] Straub RH. The complex role of estrogens in inflammation. Endocr Rev 2007;28(5):521–74.
[4] Huang B, Cai Y, Li N, et al. Sex-based clinical and immunological differences in COVID-19. BMC Infect Dis 2021;21(1):647.
[5] Edelman A, Boniface ER, Benhar E, et al. Association Between Menstrual Cycle Length and Coronavirus Disease 2019 (COVID-19) Vaccination: A U.S. Cohort. Obstet Gynecol 2022;139(4):481–9.

[6] Baena-García L, Aparicio VA, Molina-López A, et al. Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Womens Health (Lond) 2022;18. 17455057221112237.
[7] Hillson K, Clemens SC, Madhi SA, et al. Fertility rates and birth outcomes after ChAdOx1 nCoV-19 (AZD1222) vaccination. Lancet 2021;398(10312):1683–4.
[8] Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine 2021;38:101019.
[9] L, N, L. R, O.H. M. Long Covid and menopause - the important role of hormones in Long Covid must be considered. Maturitas 2021:74.
[10] Sigfrid L, Drake TM, Pauley E, et al. Long Covid in adults discharged from UK hospitals after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. Lancet Reg Health Eur 2021;8:100186.
[11] Schoenbaum EE, Hartel D, Lo Y, et al. HIV infection, drug use, and onset of natural menopause. Clin Infect Dis 2005;41(10):1517–24.
[12] Kurmanova AM, Kurmanova GM, Lokshin VN. Reproductive dysfunctions in viral hepatitis. Gynecol Endocrinol 2016;32(sup2):37–40.
*[13] Maher M, Keeffe AO', Phelan N, et al. , *Female Reproductive Health Disturbance Experienced During the COVID-19 Pandemic Correlates With Mental Health Disturbance and Sleep Quality*. Front Endocrinol 2022:**13**.
[14] Phelan N, Behan LA, Owens L. The Impact of the COVID-19 Pandemic on Women's Reproductive Health. Front Endocrinol (Lausanne) 2021;12:642755.
[15] Kwak Y, Kim Y, Baek KA. Prevalence of irregular menstruation according to socioeconomic status: A population-based nationwide cross-sectional study. PLoS One 2019;14(3):e0214071.
[16] Maity S, Wray J, Coffin T, et al. Academic and Social Impact of Menstrual Disturbances in Female Medical Students: A Systematic Review and Meta-Analysis. Front Med (Lausanne) 2022;9:821908.
[17] Uguz F, Sahingoz M, Kose SA, et al. Antidepressants and menstruation disorders in women: a cross-sectional study in three centers. Gen Hosp Psychiatry 2012;34(5):529–33.
[18] Bae J, Park S, Kwon JW. Factors associated with menstrual cycle irregularity and menopause. BMC Womens Health 2018;18(1):36.
[19] Adcock CJ, Perry LA, Lindsell DR, et al. Menstrual irregularities are more common in adolescents with type 1 diabetes: association with poor glycaemic control and weight gain. Diabet Med 1994;11(5):465–70.
[20] Ansong E, Arhin SK, Cai Y, et al. Menstrual characteristics, disorders and associated risk factors among female international students in Zhejiang Province, China: a cross-sectional survey. BMC Womens Health 2019;19(1):35.
[21] Davies J, Kadir RA. Endometrial haemostasis and menstruation. Rev Endocr Metab Disord 2012;13(4):289–99.
[22] Sharp GC, Fraser A, Sawyer G, et al. The COVID-19 pandemic and themenstrual cycle: research gaps and opportunities. Int J Epidemiol 2021.
[23] Malik S, Day K, Perrault I, et al. Reduced levels of VEGF-A and MMP-2 and MMP-9 activity and increased TNF-α in menstrual endometrium and effluent in women with menorrhagia. Hum Reprod 2006;21(8):2158–66.
[24] Maybin JA, Critchley HO. Menstrual physiology: implications for endometrial pathology and beyond. Hum Reprod Update 2015;21(6):748–61.
[25] Maybin JA, Murray AA, Saunders PT, et al. Hypoxia and hypoxia inducible factor-1α are required for normal endometrial repair during menstruation. Nat Commun 2018;9(1):1–13.
[26] Chadchan SB, Popli P, Maurya VK, et al. The SARS-CoV-2 receptor, angiotensin-converting enzyme 2, is required for human endometrial stromal cell decidualization. Biol Reprod 2021;104(2):336–43.
[27] Teuwen L-A, Geldhof V, Pasut A, et al. COVID-19: the vasculature unleashed. Nat Rev Immunol 2020;20(7):389–91.
[28] Fatimazahra M, Harras ME, Bensahi I, et al. Ovarian vein thrombosis after coronavirus disease (COVID-19) mimicking acute abdomen: two case reports. J Thromb Thrombolysis 2021;52(2):493–6.
[29] Khan SM, Shilen A, Heslin KM, et al. SARS-CoV-2 infection and subsequent changes in the menstrual cycle among participants in the Arizona CoVHORT study. Am J Obstet Gynecol 2022;226(2):270–3.
*[30] Ding T, Wang T, Zhang J, et al. Analysis of ovarian injury associated with COVID-19 disease in reproductive-aged women in Wuhan China: an observational study. Front Med 2021:286.
[31] Li K, Chen G, Hou H, et al. Analysis of sex hormones and menstruation in COVID-19 women of child-bearing age. Reprod Biomed Online 2021;42(1):260–7.
[32] Ning, J., W. Li, Y. Ruan, et al., *Effects of 2019 novel coronavirus on male reproductive system: a retrospective study.* 2020.
[33] Li D, Jin M, Bao P, et al. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA Netw Open 2020;3(5). e208292-e208292.
[34] Holtmann N, Edimiris P, Andree M, et al. Assessment of SARS-CoV-2 in human semen—a cohort study. Fertil Steril 2020;114(2):233–8.
[35] Ku J-H, Yim Y-S, Lee C-H, et al. The Preventive Effect of Systemic Treatment with Interferon-${\alpha} 2B $ for Infertility of Mumps Orchitis. Clin Exp Reprod Med 1999;26(1):111–6.
*[36] Coperchini F, Chiovato L, Croce L, et al. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev 2020;53:25–32.
*[37] Orvieto R, Segev-Zahav A, Aizer A. Does COVID-19 infection influence patients' performance during IVF-ET cycle?: an observational study. Gynecol Endocrinol 2021;37(10):895–7.
[38] Wang M, Yang Q, Ren X, et al. Investigating the impact of asymptomatic or mild SARS-CoV-2 infection on female fertility and in vitro fertilization outcomes: A retrospective cohort study. EClinicalMedicine 2021;38:101013.
[39] Prasad S, Tiwari M, Pandey AN, et al. Impact of stress on oocyte quality and reproductive outcome. J Biomed Sci 2016;23(1):1–5.
[40] Gordon JL, Balsom AA. The psychological impact of fertility treatment suspensions during the COVID-19 pandemic. PLoS One 2020;15(9):e0239253.
[41] Hu W, Zhu Y, Wu Y, et al. Impact of COVID-19 pandemic on the pregnancy outcomes of women undergoing assisted reproductive techniques (ARTs): a systematic review and meta-analysis. J Zhejiang Univ-SCI B 2022;23(8):655–65.

[42] Banker M, Arora P, Banker J, et al. Impact of COVID-19 pandemic on clinical and embryological outcomes of assisted reproductive techniques. J Hum Reprod Sci 2022;15(2):150.
[43] Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. Bmj 2020:**369**.
[44] Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, riskfactors, and maternal and perinatal outcomes of coronavirus disease 2019 inpregnancy: living systematic review and meta-analysis. Bmj 2020;370.
*[45] Eskenazi B, Rauch S, Iurlaro E, et al. Diabetes mellitus, maternal adiposity, and insulin-dependent gestational diabetes are associated with COVID-19 in pregnancy: the INTERCOVID study. Am J Obstet Gynecol 2022;227(1):74. e1-74. e16.
*[46] Vousden N, Bunch K, Morris E, et al. The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: a national cohort study using the UK Obstetric Surveillance System (UKOSS). PLoS One 2021;16(5):e0251123.
[47] Knight, M., K. Bunch, A. Cairns, et al., *Saving Lives, Improving Mothers' Care Rapid Report 2021: Learning from SARS-CoV-2-related and associated maternal deaths in the UK June 2020-March 2021*. 2021, Oxford, UK.
[48] *Coronavirus (COVID-19) Infection in Pregnancy* R.C.o.O.a. Gynaecologists, Editor. 2022.
[49] Musa SS, Bello UM, Zhao S, et al. Vertical transmission of SARS-CoV-2: a systematic review of systematic reviews. Viruses 2021;13(9):1877.
[50] Walker KF, O'Donoghue K, Grace N, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG: Int J Obstet Gynaecol 2020;127(11):1324–36.
[51] Konstantinidou, A., S. Angelidou, S. Havaki, et al., *Stillbirth due to SARS-CoV-2 placentitis without evidence of intrauterine transmission to fetus: association with maternal risk factors.* Ultrasound in Obstetrics & Gynecology, 2022.
[52] Dubucs C, Groussolles M, Ousselin J, et al. Severe placental lesions due to maternal SARS-CoV-2 infection associated to intrauterine fetal death. Hum Pathol 2022;121:46–55.
*[53] Wei SQ, Bilodeau-Bertrand M, Liu S, et al. The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. Cmaj 2021;193(16):E540–8.
[54] Edelman A, Boniface ER, Male V, et al. Association between menstrual cycle length and covid-19 vaccination: global, retrospective cohort study of prospectively collected data. BMJ Med 2022;1(1).
[55] Edelman A, Boniface ER, Benhar E, et al. Association between menstrual cycle length and coronavirus disease 2019 (COVID-19) vaccination: a US Cohort. Obstet Gynecol 2022;139(4):481–9.
[56] Trogstad, L., *Increased Occurrence of Menstrual Disturbances in 18- to 30-Year-Old Women after COVID-19 Vaccination*. 2022: Rochester, NY.
[57] Barabas K, Makkai B, Farkas N, et al. *Influence of COVID-19 pandemic and vaccination on the menstrual cycle: A retrospective study in Hungary*. Front Endocrinol 2022:**13**.
[58] Baena-García L, Aparicio VA, Molina-López A, et al. Premenstrual and menstrual changes reported after COVID-19 vaccination: The EVA project. Women's Health 2022;18. 17455057221112237.
[59] Laganà AS, Veronesi G, Ghezzi F, et al. *Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey*. Open Med 2022;17(1):475–84.
[60] Muhaidat N, Alshrouf MA, Azzam MI, et al. Menstrual symptoms after COVID-19 vaccine a cross-sectional investigation in the MENA region. Int J Women's Health 2022;14:395.
[61] Gibson EA, Li H, Fruh V, et al. *Covid-19 vaccination and menstrual cycle length in the Apple Women's Health Study*. npj Digital Med 2022;5(1):165.
[62] Skelly DT, Harding AC, Gilbert-Jaramillo J, et al. Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern. Nat Commun 2021;12(1):1–12.
[63] Turnbull AV, Rivier C. Regulation of the HPA axis by cytokines. Brain Behav Immun 1995;9(4):253–75.
[64] Hannoun AB, Nassar AH, Usta IM, et al. Effect of War on the Menstrual Cycle. Obstet Gynecol 2007;109(4):929–32.
[65] Liu S, Han J, Xiao D, et al. A report on the reproductive health of women after the massive 2008 Wenchuan earthquake. Int J Gynecol Obstet 2010;108(2):161–4.
[66] Aolymat I. A Cross-Sectional Study of the Impact of COVID-19 on Domestic Violence, Menstruation, Genital Tract Health, and Contraception Use among Women in Jordan. Am J Trop Med Hyg 2020;104(2):519–25.
[67] Aolymat I, Khasawneh AI, Al-Tamimi M. COVID-19-Associated Mental Health Impact on Menstrual Function Aspects: Dysmenorrhea and Premenstrual Syndrome, and Genitourinary Tract Health: A Cross Sectional Study among Jordanian Medical Students. Int J Environ Res Public Health 2022;19(3):1439.
[68] Demir O, Sal H, Comba C. Triangle of COVID, anxiety and menstrual cycle. J Obstet Gynaecol 2021;41(8):1257–61.
[69] Haile L, van de Roemer N, Gemzell-Danielsson K, et al. The global pandemic and changes in women's reproductive health: an observational study. Eur J Contracept Reprod Health Care 2022;27(2):102–6.
[70] Ozimek N, Velez K, Anvari H, et al. Impact of stress on menstrual cyclicity during the coronavirus disease 2019 pandemic: a survey study. J Women's Health 2022;31(1):84–90.
*[71] Nguyen BT, Pang RD, Nelson AL, et al. Detecting variations in ovulation and menstruation during the COVID-19 pandemic, using real-world mobile app data. PLoS One 2021;16(10):e0258314.
[72] Prabowo KA, Ellenzy G, Wijaya MC, et al. Impact of work from home policy during the COVID-19 pandemic on mental health and reproductive health of women in Indonesia. Int J Sex Health 2022;34(1):17–26.
[73] Takmaz T, Gundogmus I, Okten SB, et al. The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers. J Obstet Gynaecol Res 2021;47(9):3241–9.
[74] Yuksel B, Ozgor F. Effect of the COVID-19 pandemic on female sexual behavior. Int J Gynaecol Obstet 2020;150(1):98–102.
*[75] Buran G, Gerçek E. Öter, *Impact of the awareness and fear of COVID-19 on menstrual symptoms in women: a cross-sectional study.*. Health Care Women Int 2022;43(4):413–27.
*[76] Chao M, Menon C, Elgendi M. Menstrual cycles during COVID-lockdowns: A systematic review and meta-analysis. Population 2022;3:6.
[77] Tayyaba Rehan S, Imran L, Mansoor H, et al. Effects of SARS-CoV-2 infection and COVID-19 pandemic on menstrual health of women: A systematic review. Health Sci Rep 2022;5(6):e881.

[78] Chrousos GP, Torpy DJ, Gold PW. Interactions between the hypothalamic-pituitary-adrenal axis and the female reproductive system: clinical implications. Ann Intern Med 1998;129(3):229–40.
[79] Mayerhofer A, Dissen GA, Costa ME, et al. A role for neurotransmitters in early follicular development: induction of functional follicle-stimulating hormone receptors in newly formed follicles of the rat ovary. Endocrinology 1997;138(8):3320–9.
[80] Vermeulen A. Environment, human reproduction, menopause, and andropause. Environ Health Perspect 1993;101(suppl 2):91–100.
[81] Schiavi MC, Spina V, Zullo MA, et al. Love in the Time of COVID-19: Sexual Function and Quality of Life Analysis During the Social Distancing Measures in a Group of Italian Reproductive-Age Women. J Sex Med 2020;17(8):1407–13.
[82] Caruso S, Rapisarda AMC, Minona P. Sexual activity and contraceptive use during social distancing and self-isolation in the COVID-19 pandemic. Eur J Contracept Reprod Health Care 2020;25(6):445–8.
[83] Lewis R, Blake C, Shimonovich M, et al. Disrupted prevention: condom and contraception access and use among young adults during the initial months of the COVID-19 pandemic. An online survey. BMJ Sex Reprod Health 2021;47(4):269–76.
[84] Miller HE, Henkel A, Leonard SA, et al. The impact of the COVID-19 pandemic on postpartum contraception planning. Am J Obstet Gynecol MFM 2021;3(5):100412.
[85] Steenland MW, Geiger CK, Chen L, et al. Declines in contraceptive visits in the United States during the COVID-19 pandemic. Contraception 2021;104(6):593–9.
[86] CDC. *Long COVID - Household Pulse Survey - COVID-19*. 2022 [cited 2023 10/01/2023]; Available from: ⟨https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm⟩.
[87] Al-Najjar MAA, Al-Alwany RR, Al-Rshoud FM, et al. Menstrual changes following COVID-19 infection: A cross-sectional study from Jordan and Iraq. PLoS One 2022;17(6):e0270537.
[88] Stewart S, Newson L, Briggs TA, et al. Long COVID risk - a signal to address sex hormones and women's health. Lancet Reg Health Eur 2021;11:100242.